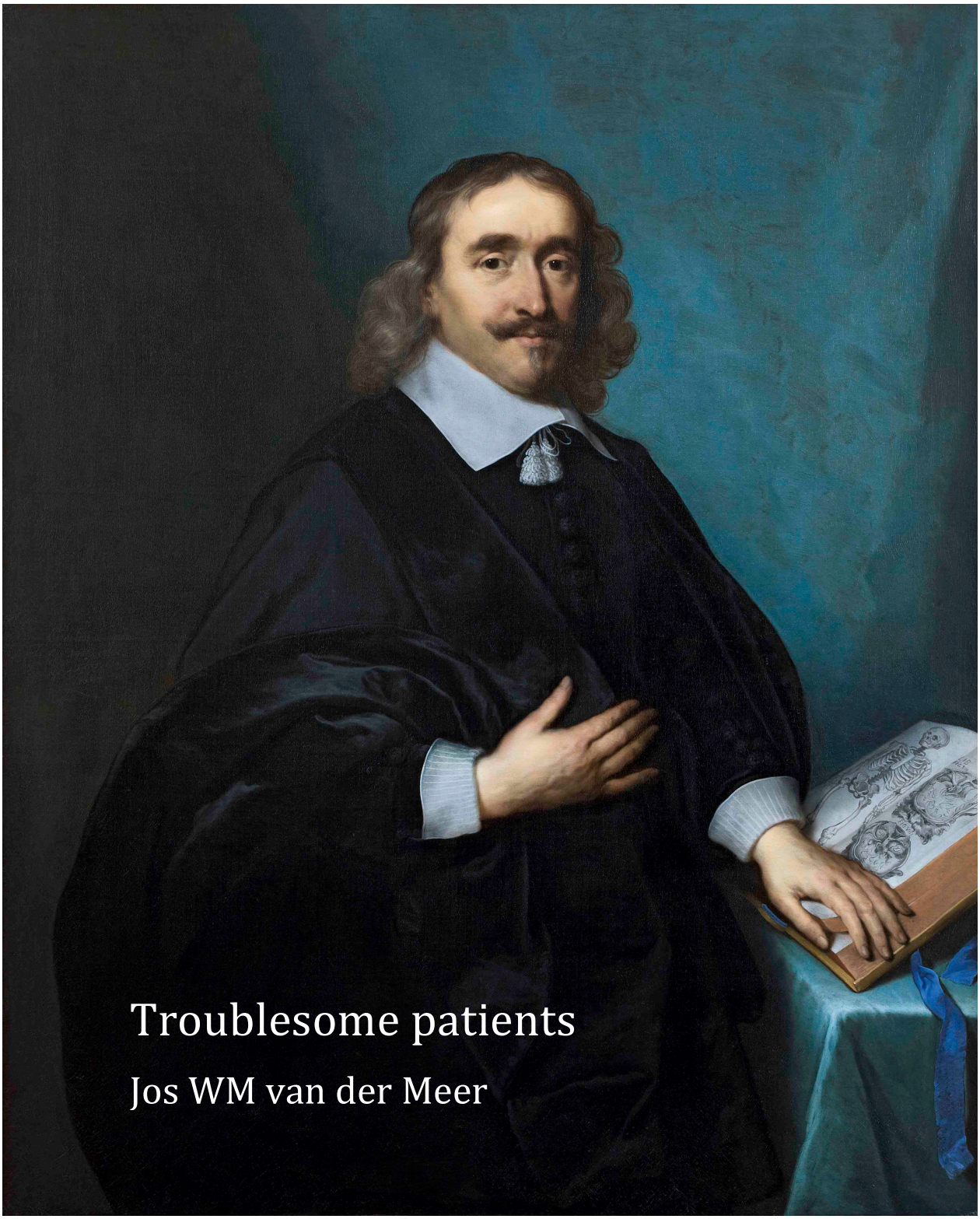

Troublesome patients

Jos WM van der Meer

Rector magnificus, Ladies and Gentlemen,

Long ago, there was a famous plague doctor in Nijmegen. His name was Ysbrand van Diemerbroeck. This is how I started my inaugural lecture at this university on the third of November 1989.
In this valedictory lecture, I also would like to start with Van Diemerbroeck.
Since two years, the Museum Het Valkhof in Nijmegen has a magnificent portrait of Van Diemerbroeck, painted by Cornelis Jonson van Ceulen (see cover). The purchase was made possible by the Rembrandt Society and also through financial support of the professors of the UMC.
Van Diemerbroeck was born in 1609 and studied philosophy and medicine in Leiden. In 1635 he settled in Nijmegen where he was facing a huge epidemic of the plague. A maximal confrontation with troublesome patients: no effective treatment and 80% mortality. He appears to be a passionate clinical investigator; he observes meticulously en describes his finding in 120 patients in his famous Tractatus de peste.
With his clinical observations he is ahead of his time. Boerhaave, the icon of modern bedside medicine, is not born until 30 years later.
Van Diemerbroeck describes treatments that we can easily classify as ineffective. It concerns experience-based medicine, nowadays still considered a slippery slope in medicine. As one of my mentors, the late, distinguished clinical pharmacologist Herman Mattie, taught me: 'We make the same mistake a thousand times and call it clinical experience'. Indeed, also in patients that are not particularly troublesome, we rely - because of a lack of evidence - often on clinical experience. So we have to stay critical and ask: Am I making the same mistake again?
Concerning troublesome patients, those that challenge the doctor with a troublesome problem, evidence for an effective approach is scanty. If the solution would be straightforward and is supported by scientific evidence, the problem becomes considerably less troublesome. I do not imply, however that evidence-based medicine is easy.
In the past years, a large number of troublesome patients was referred to me, braintwisters challenging the frontiers of our knowledge. This has converted my outpatient clinic into a collection of curiosities, but at the same time, it became a fantastic source of inspiration.
In this valedictory lecture, I would like to present a number of troublesome patients.

First, I would like to make some general remarks on the diagnostic process. It is known that the chance of a diagnosis at an outpatient clinic for internal medicine is some 66%. The modern articulate patient without a diagnosis will not be satisfied. He searches the Internet and will finally make his way to a university outpatient clinic like ours, again with a relatively small chance of success. He will bring extensive correspondence of the previous doctors, X-ray investigations on DVD and printouts from the Internet. The internist in the UMC, usually at the outpatient clinic for General Internal Medicine, will scrutinize these data, and will spend considerably more time than his predecessors, searching for the needle in the haystack. This internist should have asked the patient about his expectations, because this is important for the final satisfaction of the patient. This quest demands a lot from the internist, including quite an investment in time. I have named this the Academic Diagnostic Process (ADP). Although ADP can be seen as a magnificent challenge it has a number of tragic aspects.

- The chance that it will yield a diagnosis is small.
- The doctor must resist the temptation to start and order all kinds of (repeated) investigations, of

which it is clear at the onset, that the chance that these will contribute to a diagnosis is negligible.
• If no diagnosis is made indeed, it will demand much time and skills of the doctor to convince the patient that a further search is not a sensible thing to do.
• If the reimbursement system does not drastically change, these patients are far from profitable for the hospital. ADP is not considered as part of the profile of academic medicine and does not qualify for the Academic Component within the reimbursement system. ADP is generally more time consuming and is a greater challenge for the doctor than a patient referred with a solid diagnosis.
I feel supported by dr. Lisa Sanders, who -in her book *Every patient tells a story* - makes a plea to give ample time to listen what the patient tells us. Elsewhere I have dealt with the question, why doctors nowadays take so little time for the patient's history and the physical exam, and why they compensate this by ordering expensive additional investigations.

Van Diemerbroeck did not have a treatment for this severe bacterial infection, the plague. The situation that there is no effective treatment for bacterial infections, continued until some 70 years ago. Many fear that untreatable bacterial infections will be common in the not too distant future. The once easy-to-treat patients become troublesome patients.

A 56-year old man is admitted because of a myocardial infarction and cardiac failure.
The infarction involves the papillary muscles of the mitral valve and one of these ruptures. A prosthetic valve is inserted and post-operatively, the heart is supported by a balloon pump. On day 11 the patient has a high fever. Blood cultures yield a nosocomial bacterium of ill repute, Acinetobacter baumanii, resistant to many antibiotics, including ciprofloxacin and carbapenems. He is treated with colistin and daptomycin. Colistin is an old drug that became obsolete because of toxicity and limited activity, but it is in its second youth because it shows activity against resistant bacteria. Daptomycin is a relatively new antibiotic.
The patient seems to respond, but 5 days later he develops sepsis. The antibiotics are changed (colistin, tigecycline en fosfomycin). The blood culture now yields a totally resistant Klebsiella. The patient dies 3days later.

A sobering thought, this is a patient in Greece, presented to me by dr. Evangelos Giamarellos. But it will not take long until we will see these kinds of patient more and more in the Netherlands. There is more than a financial euro crisis. How did we arrive here? Last year, we published with a group of international an alarming article in The Lancet entitled: *'Society's failure to protect a precious resource: antibiotics'*. The question is: where did society fail. The answer is simple: precious antibiotics are prescribed for humans and animals too often, wrongly, too many and too long, and hygiene in hospitals falls short. An additional concern is that the development of new antibiotics is stagnant.
Regarding resistance, the Netherlands and Scandinavia are favourable exceptions in Europe, but also here resistance is on the rise. NethMap, the yearly report of the Dutch Working Group on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid, SWAB) warns for this development. Selection pressure by antibiotics is the cause. Also in the Netherlands antibiotics are often prescribed unnecessarily. Not only professionalism of prescribers is a problem, also behavioural aspects play an important role.
Compared to other countries, there is much attention for hospital hygiene in the Netherlands, but also here much is to be gained regarding discipline.
Despite much effort of the national Working Party for Infection Prevention (WIP), hospital

hygiene remains a tenacious problem. Recent investigations in Dutch hospitals showed that health care workers washed or disinfected their hands in less than 20 % of the recommended situations. Measures to prevent surgical infections are complied with in a minority of procedures. From the point of view of patient safety this is a shame!

A third factor that contributes to resistance problems is antibiotic use in agriculture. Here the Netherlands scores badly, with the highest antibiotic use in animals in Europe. So far little action has been taken. Which measures are needed?
1. The urgency of the resistance problem should be made crystal clear to every health care worker and consumer.
2. We should more actively combat unnecessary prescribing of antibiotics (as in viral infection, bronchitis, otitis). The SWAB guidelines are leading here.
3. Regarding hospital hygiene, we should implement zero-tolerance towards workers that do not comply with the agreed guidelines. This demands more involvement of Health Inspectorate.
4. To prevent that resistance arises against the last-resort antibiotics for multi-resistant bacteria, prescribing of those antibiotics should be restricted to doctors with special expertise (infectious disease specialists and clinical microbiologists): a *license to kill*. Activities of infectious disease specialists to combat emergence of resistance should be reimbursed.
5. Clinical microbiologists must search for resistant bacteria in a standardised fashion in the material from patients. To install an obligation to report multi-resistant bacteria (within the Law on Public Health) is urgent. Resistance rates en antibiotic usage data in hospital should become quality indicators.
6. Regarding antibiotic usage in the veterinary area we must follow the example of Denmark, where strict rules are being maintained through a high quality control system. The fear that without antibiotics agriculture, food production and economy are in danger is unfounded, given the Danish experiences.
Time runs short and we must act now to prevent that virtually all patients with a bacterial infection become troublesome patients.

In hospital hygiene, we make use of our current concepts about transmission of microorganisms between patients. That transmission often occurs via the contaminated hands of the healthcare worker. That is how hand hygiene works!
Although Van Diemerbroeck describes ‘pestilens seminarium’ – in the Du Buisson's Dutch translation ‘pestilentiaal zaat’ –, he had no idea of microorganisms. Not until 1667, Antoni van Leeuwenhoek would see bacteria through his microscope. In the days of Van Diemerbroeck, there were thoughts about contagion through bad air and stench of putrefaction of patients and dead bodies. Ideas about contagiousness of plague were already exploited in biological warfare: in Theodosia in 1346 Mongolian besiegers catapulted the bodies of those who died from plague over de walls into the city. Thus, they had a notion of contagion and transmission, without a vision of microorganisms.
A century before Van Diemerbroeck, there was somebody who perhaps understood the microbial origin: Gitolamo Fracastoro. In a poem on syphilis he postulates ‘semina’, seeds that transmit the disease. It is unclear whether he envisaged live organisms.
The observations of besiegers, of doctors like Van Diemerbroeck en Fracastoro and gifted investigators such as Van Leeuwenhoek did not come together: It would last until the 19th century before the germ theory took hold. We cannot blame these men. Information exchange and spread of scientific knowledge was very limited and even within the first academies of

sciences like the Royal Society en Leopoldina, the scientific climate was not always vibrant.

But also nowadays with easy access to scientific knowledge, it is not obvious that logical connections are made. As one of our - slightly controversial contemporary philosophers[1] says: "You do not see it until you see through". A recent example:
In our laboratory, an experiment was performed with white blood cells of students that received BCG vaccination several weeks before. As expected their white blood cells would produce more of the important defence protein interferon-γ when these cells were exposed to BCG in vitro. As a consequence of the vaccination, immunological memory had been built up against BCG. Unexpected was, that cells also after exposure to other stimuli (such as unrelated bacteria) started to produce more interferon-γ, and remained to do so long after the vaccination. Professor Mihai Netea saw this, checked whether it was true, and explored the literature. How was it possible that this simple non-specific immunity suddenly showed an enhanced function?
As he always has done over the past 21 years, he entered my office at the end of the day to show me the data. The phenomenon was seen before in mice, but also in lower animals like insects, fish and coelenterates (and as detected later also in plants)! These lower animals do not have a specific immune system, thus a bit of memory in the non-specific defence is a welcome bonus. But also mammals have this capacity. The observation that children vaccinated with BCG are not only less susceptible to tuberculosis, but also to other infections, could be explained this way. The practical importance of the phenomenon (in the meantime coined as trained immunity by professor Netea) becomes clear. Gradually we start to understand how trained immunity works.

You do not see it, until you see through. Hidden in the literature we can find the phenomenon trained immunity. How privileged we are in the e-era! Until the mid eighties, searching the literature was very time consuming.
If you were dealing with a troublesome patient - somebody, for whom you could not make a diagnosis with the help of a good textbook of medicine - you had to liberate yourself to go into the library and screen the Cumulated Index Medicus of recent years for relevant keywords. You had a chance to find titles of articles that might lead you to a diagnosis. Today, in Pubmed and even in Google, you will get suggestions from the literature within seconds, when you type the search terms relevant for the particular patient; abstracts and often full papers are right there. Weed has called this problem-knowledge coupling.
An example: A 60-year old man visits an internist with recurrent fevers, skin rash (so called urticaria) en myalgia. In the blood, a paraprotein has been found. When we type ‘fever urticaria paraprotein’ in Google of in Pubmed, the diagnosis ‘Schnitzler syndrome’ emerges, a diagnosis unknown to many doctors.
The feasibility to make a diagnosis with Google has been investigated. Doctors make the right diagnosis with the aid of Google in more than half of the cases that were presented to them. Laymen score much worse. Knowledge is needed for a productive search. Patients better avoid this kind of searching. They often make the wrong diagnosis and they encounter frightening diagnoses that do not apply to them. Just aside: we know very well that doctors, when it concerns themselves often make the wrong diagnosis.

These search strategies are important for doctors. This implies that doctors should publish

[1] Meant is the famous former soccer player Johan Cruyff

diagnosed troublesome cases in case reports. These kinds of publication are often regarded with disdain. Still they witness the fascination for the clinical problem and often form the start of further investigation. Professor Jan Vandenbroucke has pointed this out repeatedly. As doctors, we are privileged that the inspiration for further research is often close at hand, namely at the bedside. Also Van Diemerbroeck did see this.

The example of Schnitzler syndrome was not a coincidence. In 2005, we attempted, driven by despair, anakinra treatment in a patient with Schnitzler syndrome. The response was spectacular. As said, Schnitzler syndrome is characterised by attacks of fever (twice a week in our patient) with a nasty skin rash, pain and malaise. Dr Anna Simon, professor Joost Drenth and I had quite some experience with periodic fevers. In the meantime, these diseases in which inflammation is directed towards the own body had be named autoinflammatory diseases. Schnitzler syndrome was not yet in the list.
Clinical investigators in Bethesda, London en we had discovered that a number of autoinflammatory diseases respond well to interleukine-1 receptor antagonist. Interleukine-1 receptor antagonist is a natural inhibitor of inflammation that works by blocking the effect of the inflammatory mediator, the cytokine interleukin-1. With recombinant technology this substance became the drug anakinra. That anakinra, tried as ultimum refugium, would meet with such a spectacular result – not only in this troublesome case but also in a series of other patients with Schnitzler syndrome – was unexpected. It taught us that the cytokine interleukin-1 is the villain in this disease. Through investigations with a monoclonal antibody against interleukine-1β done by Heleen de Koning we now know that it concerns interleukine-1β in Schnitzler syndrome.

These experiences taught us a lot. Anakinra has very few side effects. It is a disadvantage that it has to be injected subcutaneously and during the first weeks that may lead red spots at the injection site. Anakinra has a short half-life and here I quote our national philosopher once more: ‘every advantage has its disadvantage’. Although the advantage in Schnitzler syndrome is clear, it is a disadvantage that anakinra has to be injected daily. However, the short half-life is an advantage, when we give to see whether a patient responds. Encouraged by the success in Schnitzler syndrome and other autoinflammatory syndromes, we have tried anakinra in other febrile illnesses, in which no explanation was found after profound investigations. We do this deliberately and mostly in situations, in which many doctors would do a therapeutic attempt with high dose prednisone. The side effects of prednisone are impressive. In comparison with those, anakinra is an innocent drug. A favourable response to prednisone teaches us little: many diseases respond, but why is often unclear. A good response to anakinra teaches that interleukine-1 plays a pivotal role in the disease mechanism. We nowadays use the term anakinra-responsive diseases.

The success in Schnitzler syndrome was swift. The way from bedside to bench and back is often one that takes long. In the early eighties, I became fascinated by a familial periodic fever syndrome that we described as hyperIgD syndrome in 1984. In 1999 we learned that the defect was in the mevalonate kinase gene. Five years later we knew that anakinra works. More than 25 years later we do not understand the disease completely, so the research continues.

It is not strange that I, a physician who subspecialised in infectious diseases, got interested in febrile illnesses. In 1961 two eminent American infectious disease physicians, Petersdorf en Beeson, described the clinical problem of 'fever of unknown origin' or febris e causa ignota. Troublesome patients. They defined that it concerned patients with at least 3 weeks of fever, in

whom after a week of intensive diagnostic procedures in hospital no explanation was found. During the last 20 years, we performed quite some research in this field (I have to mention dr. Lily de Kleijn and dr. Chantal Bleeker, and in the background professor Wim Oyen and professor Frans Corstens).
Over the years we observed that the percentage of patients in whom we could find an explanation for the fever, only increased,r and now reaches nearly 50 percent. The explanation is simple: Since we have much more diagnostic armamentarium than in the times of Petersdorf en Beeson, many patients do not classify any more as fever of unknown origin: we are left with the really troublesome patients. This is a lesson in modesty and a challenge: in nearly half of the patients we are unable to find an explanation for their fever, despite all our diagnostic tools; in these patients it is a benign, mild illness, though.

Another troublesome, rare disease, that fascinates me already for 35 years, is chronic mucocutaneous candidiasis: an enigmatic disturbance of host defence with recalcitrant fungal infections of skin, nails and mucous membranes. For many years, I followed these patients with the autosomal dominant form and treated them with antifungals.
In the research into host defence against fungi we gradually understood much better how humans recognise the fungus Candida and defend themselves against it; I mention the names of Mihai Netea and Bart-Jan Kullberg. Making use of our results of investigations of the host defence in these patients, and with powerful new techniques at the Department of Genetics, we could demonstrate that the defect is in the STAT1 gene. We understand now what goes wrong in host defence, and we envisage new treatment modalities. Together with the geneticists ,we are on the track of elucidating new gene defects in other troublesome patients with host defence defects.

Up to now, I have used 'troublesome' in a sense of 'posing a difficult problem'. Are not there patients that are troublesome themselves? Perhaps patients with chronic fatigue syndrome (CFS)? Many doctors experience patients with CFS as troublesome, especially when these patients present themselves with their self-made diagnosis 'myalgic encephalomyelitis'. The past 35 years, it intrigued me, how people could become so incapacitated, often all of a sudden. By showing this interest and with an empathic approach, I succeeded virtually always to built a good doctor-patient relationship, although I could not convince every patient of the concepts of CVS that professor Gijs Bleijenberg and I developed with our PhD students, on the basis of solid research. Next week, Gijs Bleijenberg will tell more about fatigue research in his valedictory lecture. One aspect, however, I would like to discuss is the damage that charlatans do (in research and in patient care). An example was the premature claim that the virus XMRV is the cause of CVS. We were unable to find the virus in our patients, reason for some colleagues from abroad, patient-activists and some journalists to accuse us of a lack of professional skills. XMRV appears to be a laboratory artefact; apologies have not reached us yet.
Not only charlatans and colleagues that trifle with the facts are a concern.
There is a growing tendency in the media – and this concerns all fields of science – to consider scientific facts just as an opinion. Pseudoscience gets lots of room and prejudiced laymen without knowledge of the matter are offered the opportunity to voice private opinions. It will be difficult to turn this tide. We must keep our trust in critical, scientifically trained journalists and columnists.

The original title of this lecture was: No focus, but still mass[2]. I may be blamed for lack of focus. Thereby, I may have fulfilled my task as a professor in general internal medicine quite well. Also in this lecture I have changed the focus several times.
Almost everybody with an opinion on science feels that one can only be successful with focus. Would I have been more successful as a scientist, clinician and teacher with more focus? I doubt it. Perhaps I am more a decathlete (as professor Frits van Oostrom has characterised the general internist)? The more elementary question is of course whether we would have made more progress with our research on hyperIgD syndrome or on chronic mucocutaneous candidiasis, had I had more focus. I doubt it: techniques necessary for a breakthrough have to be there, time has to be ripe. To my mind, it is more important to be tenacious, because science cannot be forced.

Ladies and gentlemen students, we may be proud of our Nijmegen curricula,
This is witnessed by the fact that our students attain the highest scores in the comparative inter-university exam. My contribution to that has been limited. With some satisfaction, I look back upon the introduction of the so-called clinical problem analysis in the Nijmegen curriculum. With professor Pieter de Vries Robbé, professor Paul Stuyt and dr. Cor Postma we developed this method, in which we did not worry so much how doctors think, but more about how doctors should think. Of great importance for a good problem analysis is to collect and digest the right data from the patient contact. Good history taking and a correctly executed physical exam are essential. In that respect, I am very happy that I was able to join the book Anamnese en Lichamelijk Onderzoek (History taking and physical examination) together with professor Jan van der Meer, the book that he started with my predecessor professor Ab van ’t Laar. We are working on the next edition.
Less enthusiastic I am, in retrospect, about teaching and learning in small groups:
Teacher devouring, a limited challenge for intensive studies, not very inspiring, with little contribution to solid knowledge and rapidly worn out.
We – I was also responsible for that – said farewell too early and too drastically too good clinical lectures; we did so before the mirror neurons were discovered.
As students, you see too few challenging and troublesome patients, those brain twisters I mentioned. I would like to make a plea for a UMC-broad Clinical conference, following the classic example of the Massachusetts General Hospital in Boston with the troublesome casus pro diagnosi.

Because of an increase in the issuing of rules, bureaucracy and fuss regarding the National Training fund (Opleidingsfonds), being the chief of the residency programme has become more complicated and time consuming. A gain is that we are more conscious of training the residents, and practical situations are better exploited as educational tools.
With professor Jacqueline de Graaf as chief of the residency programme, I trust that our Nijmegen internal medicine residency program will remain in the forefront of innovation, patient orientation, connection to science, and educational climate. Perhaps still time for a message from this old-fashioned doctor: Don't let your patients 'swim', support them when they are uncertain, be clear and convincing, and above all: treat the patient the same way as you wish that your next of kin are to be treated.
Having arrived at the end of my lecture, I would like to extend some words of gratitude. First of

[2] This refers to the science policy in this country where the adage was: focus and mass

all, I would like to thank the troublesome patients for the inspiration they have brought to me. Over the years I have got strong ties with many patients; often I functioned more as a coach or a counsellor.
Isaac Newton (1643-1727) said: 'If I have seen further, it is by standing on the shoulders of giants'. I would refer to the biomedical giants in history, but also closer to home: my teachers. First of all, there were my father and mother who taught my brother and me what it meant to be a doctor. I owe a lot to my medical teachers in The Hague and Leiden.
A special word of gratitude to Charles Dinarello, my mentor and good friend since 1984. I do not have to say this in English, because he claims to understand enough Dutch by now. I will not dwell upon all the things he taught me. The months that he spends yearly in Nijmegen are an enormous enrichment.

I would to thank the Board of the Radboud University Nijmegen the board of the UMC for trust, support, friendship en signs of appreciation. I realise that I might belong to the troublesome professors.
With too many to mention by name at this university and UMC, I have worked together in harmony. I am grateful for that. I have to acknowledge my 72 former PhD students. Here I should mention the 9 Indonesian scientists that did their PhD with me within the fruitful collaboration with Indonesia. In the framework of this collaboration, I have to acknowledge my good friends, Professor Robert Djokomoeljanto, Professor Ron Nelwan, Professor Sangkot Marzuki, president of the Indonesian Academy of Sciences and Director of the prestigious Eijkman Institute.

A very special period was the 6 years of vice presidency of the Royal Netherlands Academy of arts and Sciences (KNAW). The Board under the presidency of Van Oostrom and that under the presidency of Dijkgraaf meant great intellectual challenges; chairing the Assembly of the Science Department was also a great challenge every time. The great fellowship and friendship in these boards I very much cherish. The period I served on the board of the Academy was well spending albeit time-consuming. As a consequence I had less time to spend on the Department of Internal Medicine, and I am grateful to everyone in the department that they made this possible - despite an occasional grunt at the secretariat. It was possible due to the fact that we have such a great department. Everybody is working very hard, and that makes that we excel in all our core tasks and measure up to any department of internal medicine in the country.
In 1992, I was allowed to take over this magnificent department from my professor Ab van 't Laar. I tried to continue his style of leadership: 'reticent leadership'. I am not sure whether I succeeded in that. My intention to have all associate professors at that time to be made full professors worked out well and it makes that the department is ship under full sail. At this point, I would like to thank the section heads and professors for their efforts, support and friendship: Jacques Lenders, Anton Stalenhoef, Jacqueline de Graaf, Gerard Rongen, Cees Tack, André van der Ven, Bart-Jan Kullberg, Mihai Netea. A similar word of gratitude I would like to address to the other internists and also to the nursing staff. I also thank our professors that have left because of retirement (Theo Thien, Jos Lutterman, Wil Dolmans, Paul Stuyt) or because of a higher duty (Frank Gribnau, Paul Smits).
In 2008, Emile Lohman gave us a new UMC structure, a masterstroke that gave new chances to the departments. To get our own manager of the department turned out to be an absolute blessing, especially since we got Fons Verstralen. Fons, if you had been there since1992 we had been in even better shape.
When I took over in 1992, we had quite a financial deficit, and I have always said that I would

leave the department in a similar state. That created rest of mind within the department. Through your activities, Fons, I will not succeed leaving with a deficit. You are a financial and managerial hero (although I think I taught you a somewhat more daring managerial style); In addition you have become a great friend. Our executive could not have functioned without the critical input of the deputy chief, professor Jacques Lenders. Jacques, your straight control of quality, your indomitable working power, your temperament, your outspoken opinions and your exemplary role as a physician make that the department will miss you incredibly in November!
Under the governance of our former dean Frans Corstens, the organisation and finance of the research in the UMC was profoundly reconstructed. You can read that in detail in the written version of his valedictory lecture.
I had the privilege to become director of the Nijmegen Institute for Infection, Inflammation and Immunity, N4i, and become part of the Research Council; together with the dean and the other directors of the research institute this allowed me to help and organise research in the UMC. I would like to thank dr. Nathalie Bovy who as a managerial director of N4i gave splendid support and was able to guide us through the mid-term review.
The success of our own research, we owe to many, some of whom I already mentioned. A special word of thanks to dr. Leo Joosten, head of our Laboratory for Experimental Medicine, who forms a platinum team with professor Mihai Netea.
I would like to thank all our technicians, especially Johanna van der Ven-Jongekrijg, Trees Jansen, Liesbeth Jacobs en Ineke Verschueren, without whom there would not have been cytokine research here.
For many years, our research lab was stowed away in the cellars of the NIG building and we were fobbed off with the promise of a better location. Since 2011, we have got this magnificent refurbished laboratory on the second floor (and I have to acknowledge Frans Corstens again). I consider myself fortunate to be able to continue with research.

Fig. 1. Geranium. (watercolour by JWM van der Meer, 1960)

Without a professional secretariat a department is helpless. I would like to thank Miriam Wolthuis and the whole team for all their efforts. I owe quite a bit to Patricia Renkens-Broekman for her perfect support of the residency programme.
With an overfull calendar, a reliable personal assistant who does not know exactly when office hours are over, is invaluable. Geeralien Derksen-Willemsen facilitated my life and also spent countless hours organising this farewell. My gratitude cannot be expressed in words.
And now? The future of the department is bright! I praise the committee for my succession for their choice of professor Jan Smit from Leiden. Dear Jan, the past months you have been in Nijmegen at least once a week to prudently settle into the job. We are delighted with your coming. A positive development is that with your arrival the department will merge with the department of Endocrinology; for both departments a positive choice. I thank professor Ad Hermus for his loyal commitment.

Rector magnificus, after having painted a geranium in watercolour when I was 13 years old[3], I have little affinity to this plant, so please don't worry (Fig. 1). There is so much challenge still in science, teaching, medicine and art. I will not have many dull moments.

Dear Mechtilde, our life together since the Golfe de Santa Manza has been characterised by great happiness. I cannot express how grateful I am for your love, support and patience in the past years. I look very much forward to the years in front of us.
There is quite some warning against late parenthood, and medically that is true. It is however a blessing to have relatively young children, children that make us enormously proud. Hanna and Jonathan, you two make our lives incredibly precious!
This is what I had to say.

[3] Sitting behind the geraniums is a Dutch expression for being retired and sitting around waiting to die.